II. Remarks

A. Amendments to the Claims and Formal Matters

Claims 62, 66-71 and 75-82 and 87-93 are pending in this application. Claims 87 and 90-92 have been withdrawn by the Examiner. Claim 62 is proposed herein to be amended. Claims 95-99 are newly added. Claims 87-91 are canceled with this response without prejudice to pursuing the subject matter of these claims on one or more continuing applications. Upon entry of these amendments, claims 62, 67, 68, 70, 71, 76-82, 92-93 and 95-99 will be pending with claims 62, 67, 68, 70, 71, 76-82, 93 and 95-99 under active consideration. Applicant respectfully requests entry of the amendments and remarks made herein into the file history of the present application. Paragraph numbers are cited herein with reference to the published application

Claim 62 is amended to recite a "fusion protein comprising (1) an IFNAR2 portion consisting of the sequence of SEQ ID NO: 2 and (2) an immunoglobulin portion consisting of an immunoglobulin or fragment thereof." Support for this amendment is found at [0058] of the specification which states that "MIFNAR2 EC may thus be fused to another protein, polypeptide or the like, e.g., an immunoglobulin or a fragment thereof."

Claim 62 is also amended to recite that the affinity of the fusion protein for IFN-β is synergistically increased "25 to 100-fold" compared to "the affinity of wild type human IFNAR2 for IFN-β."

Support for new claim 95 may be found throughout the specification with exemplary support at paragraph [0033].

Support for new claims 96-98 may be found throughout the specification with exemplary support at paragraphs [0066]-[0067].

Support for new claim 99 may be found throughout the specification with exemplary support at paragraph [0072].

Applicant respectfully submits that no new matter has been added by the amendment.

B. Patentability Rejections

1. The Rejections Under 35 U.S.C. §112, Second Paragraph Should be Withdrawn

Claims 62, 67, 68, 70, 71, 76-82, 88, 89 and 93 are newly rejected under 35 U.S.C. 112, second paragraph, as allegedly indefinite. Specifically, the Examiner alleges that recitation in the claims of "at least 25 to 100-fold," "at least 30 pM" and "at least 50-fold" in claims 62, 67 and 68 respectively, render the metes and bounds of the claims undefined.

While disagreeing with the Examiner that these limitations, which have appeared in the claims throughout prosecution, are indefinite, Applicants herein amend claim 62 to recite that the affinity of the fusion protein for IFN-β is synergistically increased "25 to 100-fold" compared to wild type human IFNAR2, thus setting an upper boundary on the affinity in claim 62. Because claims 67 and 68 depend from claim 62 and thus incorporate every limitation of claim 62, the amendment to claim 62 also sets an upper boundary on the affinity in these claims. Accordingly, the rejections under 35 U.S.C. 112, second paragraph, may be properly withdrawn and Applicants respectfully request such withdrawal.

2. The Rejections under 35 U.S.C. §112, First Paragraph – New Matter – Should be Withdrawn

Claims 62, 67, 68, 70, 71, 76-82, 88, 89 and 93 are newly rejected under 35 U.S.C. 112, first paragraph, as allegedly containing new matter. Solely in the interest of expediting prosecution of the present application, and in no way acknowledging agreement with the Examiner on this point, Applicants herein amend claim 1 to recite a "fusion protein comprising (1) an IFNAR2 portion consisting of the sequence of SEQ ID NO: 2 and (2) an immunoglobulin portion consisting of an immunoglobulin or fragment thereof." The proposed amendment finds explicit basis in the specification as filed. Accordingly, the rejections under 35 U.S.C. 112, first paragraph relating to new matter may be properly withdrawn and such withdrawal is respectfully requested.

3. The Rejections Under 35 U.S.C. §112, First Paragraph – Enablement – Should be Withdrawn

a. Claims 62, 66-71, 75-82 and 93

Claims 62, 66-71 and 75-82 and 93 stand rejected under 35 U.S.C. §112, first paragraph, for allegedly lacking an enablement for the full scope of the invention.

Applicants herein amend claim 62 to recite a fusion protein comprising (1) an IFNAR2 portion consisting of the sequence of SEQ ID NO: 2 and (2) an immunoglobulin portion consisting of an immunoglobulin or fragment thereof. Applicants believe that these amendments overcome the Examiner's rejections.

It is straightforward to make the claimed fusion proteins using routine techniques that are well known to a person of ordinary skill in the art. Given the experimental data in the present specification concerning the synergistically enhanced affinity for IFN-β of a polypeptide of SEQ ID NO: 2 *per se*, it is reasonable to expect that the now-claimed fusion proteins comprising an IFNAR2 portion *consisting of* the sequence of SEQ ID NO: 2 and an immunoglobulin portion consisting of an immunoglobulin or fragment thereof to have the same effect. A person of ordinary skill in the art using routine techniques is capable of fusing these polypeptides in a manner that does not affect the affinity for IFN-β without recourse to undue experimentation. Moreover, fusion proteins retaining synergistically enhanced affinity for IFN-β can be easily identified by the assays disclosed in the present specification. Fusion proteins not retaining a synergistically enhanced affinity for IFN-β are outside the scope of the claims.

At any rate, Applicants respectfully point out that, contrary to the Examiner's repeated (and incorrect) assertion, the invention as now claimed does not "encompass polypeptide sequences of numerous receptor variants of the type I IFN receptors, such as membrane bound..." This is because the now claimed fusion proteins comprise an IFNAR2 portion *consisting of* SEQ ID NO: 2. As previously pointed out to the Examiner, the sequence set forth as SEQ ID NO: 2 corresponds to the IFNAR2 EC (with substitutions of H78A and N100A). As presently claimed, the fusion proteins cannot encompass other receptor variants of the type I IFN receptors because the IFNAR2

portion consists of SEQ ID NO: 2 and therefore cannot comprise additional IFNAR2 residues beyond those set forth as SEQ ID NO: 2.

Accordingly, Applicants respectfully submit that the full scope of the rejected claims is enabled by the present disclosure and request that the Examiner withdraw the rejection for lack of enablement.

b. Claims 88 and 89

Claims 88 and 89 stand rejected under 35 U.S.C. §112 for an alleged lack of enablement for the reasons of record.

Applicants cancel claims 88 and 89 with this amendment thus rendering these rejections moot. Accordingly, Applicants respectfully request that the rejections of claims 88 and 89 under 35 U.S.C. §112 be withdrawn.

4. The Rejections Under 35 U.S.C. §103(a) Should be Withdrawn

a. Claims 62, 66-71 and 75-76

Claims 62, 66-71 and 75-76 stand rejected under 35 U.S.C. §103(a) over Piehler *et al.* ("Piehler"). The invention as now claimed specifies that the affinity of the claimed fusion protein for IFN-β is synergistically increased "25 to 100-fold" compared to wild type human IFNAR2. Such an increase in affinity is neither taught nor suggested by Piehler et al.

As a preliminary matter, Applicants wish to reiterate that what is claimed is a fusion protein wherein the affinity for IFN-β is synergistically increased 25 to 100-fold **compared to wild type human IFNAR2**. Although Applicants believe that claim 62 has clearly defined the invention as discussed above throughout the prosecution history of the present application, Applicants herein amend claim 62 to recite that the affinity of the now claimed fusion protein for IFN-β is synergistically increased 25 to 100-fold compared to "the affinity of wild type human IFNAR2 for IFN-β."

The Examiner states at page 9 of the Office action:

> Piehler et al. further predicted a 20-fold tighter binding for IFNβ compared to IFNα2, in the INFAR2 receptor harboring both mutations. Piehler et al. state that IFNα2 and IFN-β bind competitively to the same functional epitope (second column, p. 234) and that the N100A mutation hardly affects the binding of IFNa2, and the H78A destabilizing the complex with IFNα2 only twofold (first column, p. 230); additionally stating: 'Two mutations on ifnar2 (H78 and N100) result in an increased rate of dissociation (and thus higher affinity) for IFNβ but not for IFNα2.' (first column, p. 234).

Based on this analysis of Piehler, the Examiner concludes that "Piehler et al. specifically stated that the H78A/N100A double mutant should exhibit 20-fold tighter binding for IFN-β." (OA, p. 10).

Applicants initially would like to point out to the Examiner that Piehler does not teach affinity (k_D, dissociation consant) for *either* IFNAR2 single mutant (H78A or N100A) for IFNβ. As can be seen from Table 2, Piehler teaches dissociation rates (k_d) for IFNAR mutants binding IFNβ but is unable to provide association rates (k_a). *See also*

Piehler, p. 229, 2nd col. ("The association kinetics of IFNβ significantly deviated from a simple single exponential model and was not further evaluated"). Thus, Piehler did not determine binding affinity (k_D) for either of the INFAR2 single mutant (H78A or N100A) interactions with IFNβ, neither by determining an equilibrium binding nor from calculations of the rate constants ($k_D = k_d / k_a$). In fact, the association rate constant (k_a) is not provided for any of the IFNAR2 mutants. Dissociation rate is not the same as binding affinity and is only useful as a proxy for binding affinity when the association rate remains constant, which is not shown by Piehler. In order to make any predictive statements about what the H78A/N100A double mutant may do to the free energy of binding to IFNβ, one must at least know the effect on binding affinity (k_D) of each single mutant. This binding affinity is simply not stated. Accordingly, Piehler cannot be said to provide any expectation with respect to the affinity of the presently claimed double mutant for IFNβ.

With this in mind, turning to the statement in Piehler cited by the Examiner, it is clear that this statement derives from a comparison of the dissociation rates for wild type (wt) IFNAR2 and the IFNAR2 single mutants (H78A and N100A). Indeed, Piehler concludes that an H78/N100 IFNAR2 double mutant "should have about 20-fold tighter binding for IFNβ compared to IFNα2" (emphasis added). This prediction of Piehler was made with the assumption that the effects of each single mutant on the dissociation rate of IFNβ and IFNα2 would be additive (i.e. not synergistic). To wit, Piehler teaches that the H78A mutant stabilizes the complex with IFNβ nearly 2-fold while destabilizing the complex with INFα2 more than 2-fold, corresponding to a more than 4-fold tighter binding of this mutant for IFNβ than for IFNα2 relative to wild type IFNAR2. Piehler then teaches that the N100A mutant decreases the dissociation rate for IFNβ by almost 4-fold while hardly affecting IFNα2 binding, corresponding to a 4-fold tighter binding for IFNβ than for IFNα2 relative to wild type IFNAR2. Thus, if each mutation is considered independent of the other (i.e. if the effects are considered to be additive), the double mutant would be predicted to exhibit ~16-fold tighter binding to IFNβ than for IFNα2

compared to wt INFAR2. However, the dissociation rate constant of wild type IFNAR2 for binding IFNα2 is a little higher than for IFNβ, which translates to the INFAR2 double mutant having a ~ 20-fold tighter binding for IFNβ than for IFNα2. Thus, it is clear that Piehler speculated that the effects of the two mutations would be additive. *See also* Piehler, Table 2, disclosing dissociation rate constants for wt and mutant IFNAR2. In this regard, Applicants remind the Examiner that even the possible additive nature of the mutations is pure speculation and there is no guarantee that such an effect would be observed. The skilled artisan would appreciate that introducing two mutations in close spatial proximity could just as likely result in mutual cancellation or destabilization.

In sum, the portions of Piehler cited by the Examiner teach only the relative dissociation kinetics of single IFNAR2 mutants (H78A or H100A) for IFNβ compared to the affinity of the same mutants for IFNα2 and say nothing about the affinity of an H78A/N100A double mutant for IFNβ compared to the affinity of wild type IFNAR2 for IFNβ. To the extent that Piehler discusses the free energy of binding of binding IFNβ for, *inter alia,* IFNAR2 mutants H78A and N100A, one of ordinary skill in the art, speculating that the mutations would be additive, could at best predict that an H78A/N100A IFNAR2 double mutant would demonstrate a 6-fold increase in affinity for IFNβ compared to the affinity of wild type IFNAR2 for IFNβ. *See* Piehler, Figure 8. Of course, Piehler uses the dissociation rate constant (k_d) as a proxy for k_D, as discussed above, so Piehler cannot reasonably be said to provide *any* expectation with respect to the affinity of the presently claimed double mutant for IFNβ.

As discussed by Applicants in their prior response(s), Piehler does not teach or suggest that cooperative effects would be expected in an H78A/N100A IFNAR2 double mutant. To the contrary, as discussed above, Piehler speculates that the effects of the mutations would be additive. Moreover, Piehler states generally that, although cooperative effectives among mutations cannot be ruled out, "the sum of interaction energies for individual mutations gives an estimation as to what extent the binding site is mapped by the residues investigated." Importantly, the authors conclude that "[f]or IFNα2, the sum of the interaction energies of all residues investigated is approximately

53 kJ/mol, which is close to the free energy of the complex formation." Accordingly, Piehler teaches that, for interaction of IFNAR2 with IFNα2, the sum of interaction energies for individual mutations (i.e., ignoring potential cooperative effects) provides a very good estimate of the interaction energy when such mutations are combined. Thus, one of ordinary skill in the art is not taught to expect cooperative effects to occur among IFNAR2 residues. Rather, based on Piehler's speculation that the effects of the single mutations would be additive in the double mutant, the skilled artisan could at best expect a 6-fold increase in affinity for IFNβ compared to the affinity of wild type IFNAR2 for IFNβ, as discussed above.

The present specification teaches that the affinity of the H78A/N100A double mutant is surprisingly ~100 times higher than the wild type for IFNβ and therefore demonstrates that the hypothesis posed in Piehler is incorrect, since the effects of the individual mutations are not additive, but show a dramatic and unexpected synergy which conveys real and practical therapeutic advantages. According to MPEP § 716.02(a), a demonstration of synergy is sufficient to overcome a *prima facie* case of obviousness where the results obtained are greater than those which could have been expected from the prior art to an unobvious extent and the results are of significant, practical advantage. As amended herein, the pending claims require that the affinity for IFN-β is increased 25 to 100-fold. Even if Piehler can be read to disclose the possibility of some cooperative effects, which is not admitted, an increase of 25 to 100-fold in affinity constitutes results greater than those which could have been expected from Piehler.

With respect to advantages of the H78A/N100A double mutant, Applicants direct the Examiner's attention to the post-filing date reference Peleg-Shulman *et al.*, J.B.C., 279(17), p. 18046-18053 (2004), listed on an Information Disclosure Statement submitted herewith, which describes a study in which wild type IFNAR2 and several IFNAR2 mutants including the H78A/N100A double mutant, were injected into rats along with IFNβ to assess the potential of the IFNAR2 polypeptides to act as *in vivo* carriers for IFNβ. Peleg-Shulman concludes that the affinity of the H78A/N100A double mutant for IFNβ make the double mutant an ideal carrier protein for IFNβ: "the optimal

affinity of a carrier protein [for IFNβ] would be in the low picomolar range, which is the affinity measured for ifnar2-EC H78A/N100A binding IFNβ...[i]n the case presented here, the ifnar2-EC double mutant H78A/N100A is practically the *ideal* carrier protein for IFNβ." Peleg-Shulman, p. 18053, col. 1 bridging to col. 2 (emphasis added). In this regard, Peleg-Shulman teaches that co-administration of the H78A/N100A double mutant with IFNβ resulted in (1) a dramatic increase in the concentration of IFNβ in the circulation (2) a much slower decline of IFNβ levels from serum and (3) detection of IFNβ in the plasma after extended time periods. *See* Peleg-Shulman, p. 18051, col. 1. The prior art of record, alone or in combination, does not teach or suggest that the H78A/N100A double mutant would be advantageous over wild-type IFNAR-2 as a carrier protein for enhancing the effect of IFNβ in a therapeutic context.

In light of the unexpected, claimed synergistic increase in affinity for the H78A/N100A double mutant, no indication of which is disclosed by Piehler and which could not have been obvious to the ordinary artisan, and the significant practical advantage of the increased affinity, Applicant respectfully requests that the rejection for obviousness be reconsidered and withdrawn.

b. Claims 77-82

At page 9 of the Final Office Action, the Examiner maintains his rejection of claims 77-81 under 35 U.S.C. §103(a) over Piehler and Campbell *et al.* ("Campbell") and applied this rejection to claim 82 as well. As discussed above, Piehler fails to teach or suggest the synergistic effect of the claimed double mutant H78A/N100A. Campbell, characterized by the Examiner as describing fusion protein constructs containing the hGH signal peptide in place of the native signal sequence of proteins, does nothing to remedy the defect of Piehler. Accordingly, Applicant respectfully requests that the rejection for obviousness be reconsidered and withdrawn.

C. Conclusion

In view of the above amendments and remarks, Applicant respectfully submits that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the instant application, the Examiner is encouraged to call the undersigned at the number listed below.

Respectfully submitted,

HOWREY LLP

Dated: October 9, 2009

By: /David W. Clough/
David W. Clough, Ph.D.
Registration No.: 36,107
Customer No.: 22930
Telephone No.: (312) 595-1408

HOWREY LLP
ATTN: Docketing Department
2941 Fairview Park Drive, Suite 200
Falls Church, VA 22042-2924
Facsimile No.: (703) 336-6950